IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Weiner *et al.*	Confirmation No.:	8108
Serial No.:	10/759,561	Art Unit:	1617
Filed:	January 15, 2004	Examiner:	Kim, Jennifer M.
For:	SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES	Attorney Docket No:	12560-016-999

DECLARATION OF DR. DOUGLAS W. BONHAUS

Commissioner for Patents
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Sir:

I, DOUGLAS W. BONHAUS, Ph.D., declare and state as follows:

1. I am a citizen of the United States of America, and hold the position of Vice President, Biosciences, of ACADIA Pharmaceuticals Inc. ("ACADIA Pharmaceuticals").

2. I received my Bachelor of Science degree in Physiology from Michigan State University, East Lansing, Michigan, in 1980. I received my Ph.D. degree in Pharmacology and Toxicology from the University of Arizona, Tucson, Arizona in 1983.

3. After receiving my Ph.D., I was employed as a Research Associate in the Department of Medicine at Duke University, Durham, North Carolina, from 1983 to 1987. In 1987, I was promoted to Research Assistant Professor at Duke University, and held that position until 1991. In 1991, I joined Syntex Research, Palo Alto, California, as Staff Researcher II. In 1995, I joined Roche Bioscience, Palo Alto, California, as a Principal Scientist. In 2000, I was promoted to Senior Scientist at Roche Bioscience, and held that position until 2005. In 2005, I joined ACADIA Pharmaceuticals as Vice President, Biosciences. I have published in various peer-reviewed journals and presented my research

at national and international meetings. A copy of my curriculum vitae is attached as **Exhibit 1**.

4. Currently, as Vice President of Biosciences at ACADIA Pharmaceuticals, I am involved in the process of drug development. My duties include leading ACADIA Pharmaceuticals' drug discovery efforts. This entails leading the Drug Discovery organization (screening, pharmacology, pharmacokinetics, etc.). It also includes the responsibility for identifying appropriate drug targets and selecting the best potential drug candidates that interact with these targets for further clinical evaluation.

5. I have reviewed the specification of the present application, a copy of which is attached as **Exhibit 2**. I have read the claims as rejected by the United States Patent and Trademark Office, a copy of which is attached as **Exhibit 3**. I am familiar with the Examiner's comments concerning PCT Publication No. WO 0166521 to Andersson *et al.* ("Andersson") at pages 3-5 of the Office Action dated October 10, 2007, and at pages 3-6 of the final Office Action dated July 11, 2008 (copies of which are attached as **Exhibit 4** and **Exhibit 5**). I am familiar with Andersson, PCT Publication No. WO 0166521, a copy of which is attached as **Exhibit 6**.

6. ACADIA Pharmaceuticals is currently developing serotonin-2A ("5-HT_{2A}") receptor inverse agonists for the treatment of specific neurological and psychiatric indications. In my opinion, desirable attributes of an active 5-HT_{2A} receptor inverse agonist for these indications should include: (1) high potency as an 5-HT_{2A} receptor inverse agonist; (2) lack of "off-target" activity at serotonin-2B ("5-HT_{2B}"), histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptors, as further explained below; and (3) low rates of metabolism in human microsomes because this is predictive of favorable pharmacokinetics in humans.

7. **5-HT_{2A} Receptor Inverse Agonist Activities.** Upon information and belief, cell based assays to assess the potency of test compounds for inverse agonist activity on human serotonin 5-HT_{2A} receptors were performed by or on behalf of ACADIA Pharmaceuticals using a protocol similar or identical to that described in **Exhibit 7.** Results of the 5-HT_{2A} receptor inverse agonist activity assays are provided in Table I, attached as **Exhibit 8**. The 5-HT_{2A} receptor inverse agonist activity assay results are presented as $pIEC_{50}$ values. For any given test compound, the $pIEC_{50}$ value is the negative logarithm of an IEC_{50}

value, which is the potency of the test compound as determined in an inverse agonist assay. In my opinion, compounds with $pIEC_{50}$ values less than 6.0 for a given receptor are considered to be ineffective inverse agonists at that receptor and are indicated with "NA."

8. **Exhibit 8** provides 5-HT_{2A} receptor inverse agonist activity assay results for the tartrate salt ("Example A") and the hydrochloride salt ("Example B") of the compound of Formula I of the application at issue. The $pIEC_{50}$ values for each are 9.1 and 9.4, respectively. The tested compounds with $pIEC_{50}$ values greater than 9.1 or 9.4 are more potent inverse agonists than Example A or Example B, and compounds with $pIEC_{50}$ values less than 9.1 or 9.4 are less potent inverse agonists than Example A or Example B.

9. **Exhibit 8** also provides 5-HT_{2A} receptor inverse agonist activity assay results for exemplary compounds provided in PCT Publication No. WO 0166521 to Andersson *et al.* (collectively, "the Andersson compounds"). For instance, Example 1 in **Exhibit 8** corresponds to Example 1 on page 38 of Andersson, Example 2 in **Exhibit 8** corresponds to Example 2 of page 39 of Andersson, and so forth.

10. The results provided in **Exhibit 8** indicate that out of over 100 compounds tested, only 9 compounds had $pIEC_{50}$ values equal to or greater than the $pIEC_{50}$ values of Example A (9.1) and/or Example B (9.4). Thus, Example A and Example B are among the most potent 5-HT_{2A} receptor inverse agonists. And, as will be shown below, each compound with equal or higher $pIEC_{50}$ values than Examples A and B was an inferior candidate because of off-target activity, higher rates of microsomal clearance, or both.

11. **"Off Target" Receptor Activities.** Attached as **Exhibit 9** is a copy of Weiner *et al.*, *J. Pharmacol. & Exp. Therap.*, Vol. 299, No. 1, pp. 268-76 (2001) which reports that a number of antipsychotics (*e.g.*, sertindole, clozapine) have, in addition to being 5-HT_{2A} receptor inverse agonists, activity at histamine H_1, dopamine D_2, 5-HT_{2B} and 5-HT_{2C} receptors (see Table 1 on page 272 of Weiner *et al.*). Based on my personal experience and on my review of the papers attached hereto, a selective 5-HT_{2A} receptor inverse agonist to be used as a therapy should lack activity at histamine H_1, dopamine D_2, 5-HT_{2B} and α_{1A} adrenoceptor receptors since activity at these specific receptor subtypes either have been or are believed to be associated with certain adverse effects. The papers on which I rely include Borman *et al.*, *Br. J. Pharmacol.*, Vol. 135, No. 5, pp. 1144-51 (2002), Choi *et al.*,

Development, Vol. 124, pp. 1745-1755, (1997), Fitzgerald *et al.*, *Molecular Pharmacol.* Vol. 57, pp. 75-81 (1999), Negibil *et al.*, *PNAS*, Vol. 97, No. 17, pp. 9508-13 (2000), Negibil *et al.*, *Circulation*, Vol. 103, pp. 2973-79 (2001), Negibil *et al.*, *FASEB J.*, Vol. 27, No. 10, pp. 1373-75 (2003) (5-HT_{2B} receptor), **Exhibit 10**; Kay, G.G., *J. Allergy Clin. Immunol.*, Vol. 105, No. 6, Pt. 2, pp. S622-27 (2000) (histamine H_1 receptor), **Exhibit 11**; Wirshing *et al.*, *J. Clin. Psychiatry*, Vol. 21, No. 6, pp. 579-87 (1999) (histamine H_1 receptor), **Exhibit 12;** Glazer, W.M., *J. Clin. Psychiatry*, Vol. 61, Supp. 3, pp. 16-21 (2000) (dopamine D_2 receptor), **Exhibit 13;** and Sica, D.A., *J. Clin. Hypertension*, Vol. 7, pp. 757-62 (2005) (α_{1A} adrenoceptor), **Exhibit 14**.

12. Upon information and belief, assays to assess test compounds on the 5-HT_{2B}, histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptors were performed by or on behalf of ACADIA Pharmaceuticals using a protocol similar or identical to that attached as **Exhibit 15.** Results for the compounds tested for 5-HT_{2B}, histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptor activity are provided in Table II, attached as **Exhibit 16**. In my opinion, compounds with pK_i values less than 6.0 for a given receptor are considered to be ineffective antagonists at that receptor and are indicated with "NA" (no activity).

13. Of the Andersson compounds tested, those that had little or no activity at 5-HT_{2B}, histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptors (**Exhibit 16**), also were considerably less active than Example A or Example B as an 5-HT_{2A} receptor inverse agonist (see **Exhibit 8**), or had low human microsomal stability (as shown in **Exhibit 21**, which is discussed below).

14. Significantly, the data indicate that Example A and Example B were selective for 5-HT_{2A}, that is, they had little or no activity at 5-HT_{2B}, histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptors.

15. **Intrinsic Clearance in Human Microsomes.** *In vitro* human microsomal clearance values have been used to predict *in vivo* human clearance values and even bioavailability as supported by the papers attached hereto (Ito *et al.*, *Pharm. Res.*, Vol. 22, No. 1, pp. 103-12 (2005), **Exhibit 17**; Stoner *et al.*, *Int. J. Pharm.*, Vol. 269, No. 1, pp. 241-49 (2004), **Exhibit 18**; and Naritomi *et al.*, *Drug Metab. Dispos.*, Vol. 29, No. 10, pp. 1316-24 (2001), **Exhibit 19**). In my opinion, the use of human microsomes is an established

way of predicting human oral bioavailability. Higher clearance values correspond to lower bioavailability. Further, experiments performed by or on behalf of ACADIA Pharmaceuticals using a limited number of Andersson compounds have demonstrated such a relationship between the microsomal clearance values and oral bioavailability.

16. Upon information and belief, *in vitro* intrinsic clearance assays in human microsomes were performed by or on behalf of ACADIA Pharmaceuticals using a protocol similar or identical to that attached as **Exhibit 20.** The results are provided in Table III, attached hereto as **Exhibit 21**.

17. The intrinsic clearance (CL_{int}) for Example A and Example B observed were 7 and 2 (µl/min/mg). Test compounds with CL_{int} values greater than 7 or 2 (µl/min/mg) are predicted to have less stability *in vivo* (or lower bioavailability) than Examples A or B. Compounds with CL_{int} values less than 2 or 7 (µl/min/mg) are predicted to have greater stability *in vivo* (or greater bioavailability) than Examples A or B. The CL_{int} values for Examples A and B were lower than all but two of the Andersson compounds tested.

18. Only four of the Andersson compounds that were tested were found to have similar or lower CL_{int} values than Examples A or B (i.e., Examples 58, 60, 110, 127 in **Exhibit 21**). However, these compounds were also found to have off target activity ($pIEC_{50}$ or pK_i values greater than 6.0) at one or more of 5-HT_{2B}, histamine H_1, dopamine D_2 and α_{1A} adrenoceptor receptors (*see* **Exhibit 16**), and are less potent 5-HT_{2A} receptor inverse agonists (*see* **Exhibit 8**). In other words, of the compounds found to have the best predicted oral bioavailability (lowest microsomal clearance rates), only Examples A and B are potent and selective 5-HT_{2A} inverse agonists.

19. **Conclusions.** The results provided in Tables I, II and III herein demonstrate that, of the compounds tested, Examples A and B are among the most potent 5-HT_{2A} receptor inverse agonists. Moreover, in comparison to compounds with similar potency as 5-HT_{2A} receptor inverse agonists, Examples A and B had the greatest microsomal stability and had little or no undesired off-target activity.

20. In my opinion, based on the results provided herein, the compound of Formula I and its salts are surprisingly superior as orally bioavailable selective 5-HT_{2A} receptor inverse agonists compared to any of the Andersson compounds tested.

21. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that I make those statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/14/08

Doug Bonhaus

DOUGLAS W. BONHAUS, Ph.D.